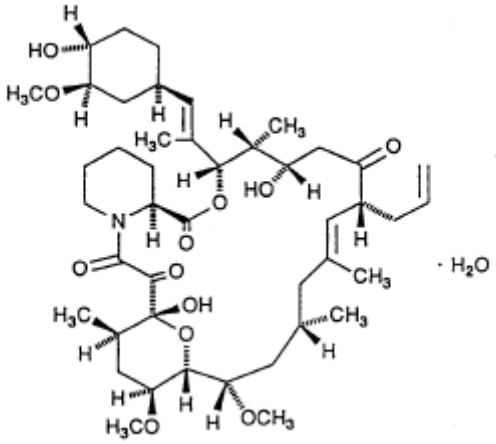
PRODUCT INFORMATION

TACROLIMUS SANDOZ®
0.5mg/ 0.75mg/ 1mg/ 2mg/ 5mg capsules

NAME OF THE MEDICINE

Tacrolimus (as monohydrate)

[3S[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19 dihydroxy-3- [2-(4-hydroxy-3-methoxycyclohexyl) -1-methylethenyl]-14, 16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15, 19-epoxy-3H-pyrido[2,1c][1,4] oxaazacyclotricosine-1,7,20, 21(4H,23H)-tetrone, monohydrate



CAS [109581-93-3]

Empirical formula: $C_{44}H_{69}NO_{12}. H_2O$ MW: 822.03

DESCRIPTION

Tacrolimus appears as white crystals or a crystalline powder, very soluble in methanol and chloroform, freely soluble in acetone and ethanol and practically insoluble in hexane and water. It is obtained by fermentation as a single enantiomer but exists in tautomeric equilibration in aqueous solution.

Excipients capsule filling:

Hypromellose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

Excipients capsule shell:

Titanium dioxide, sodium lauryl sulfate, sorbitan monolaurate, gelatin, iron oxide yellow (0.5mg, 0.75mg, 1mg & 2mg capsule only), iron oxide red (1mg, 2mg & 5mg capsule only), iron oxide black (1mg capsule only), brilliant blue FCF CI42090 (0.75mg & 2mg capsule only).

The printing ink used for the 0.5mg, 1mg and 5mg capsules contains trace amount of shellac, absolute ethanol, isopropyl alcohol, butan-1-ol, propylene glycol, ammonia, iron oxide black, and potassium hydroxide.

The printing ink used for the 0.75mg and 2mg capsules contains trace amount of either TekPrint SW-9008 black ink or TekPrint SW-9009 black ink. TekPrint SW-9008 and TekPrint SW-9009 black ink.

PHARMACOLOGY

Pharmacodynamics

Tacrolimus is a macrolide lactone with potent *in vitro* and *in vivo* immunosuppressive activity. Studies suggest that tacrolimus inhibits the formation of cytotoxic lymphocytes which are regarded as being primarily responsible for graft rejection. Tacrolimus suppresses T cell activation and T helper cell dependent B cell proliferation, as well as the formation of lymphokines such as interleukins-2 and 3 and gamma-interferon and the expression of the interleukin-2 receptor. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP) which is responsible for the intracellular accumulation of the compound. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed and the phosphatase activity of calcineurin inhibited.

Studies in animals and humans have shown that tacrolimus is able to prevent and treat graft rejection following transplantation of the liver, kidney and other solid organs.

Pharmacokinetics

Absorption

In humans, tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed.

Following oral administration of tacrolimus capsules peak concentrations (C_{max}) of tacrolimus in blood are achieved in approximately one to three hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20 to 25%.

After oral administration (0.30mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within three days in the majority of patients.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect

being most pronounced after a high fat meal. The effect of a high carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.

In a study of stable renal transplant patients who were administered tacrolimus immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus.

A strong correlation exists between AUC and whole blood trough levels at steady state. Monitoring of whole blood trough levels, therefore, provides a good estimate of systemic exposure.

Distribution and elimination

In humans, the disposition of tacrolimus after intravenous infusion may be described as biphasic.

In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/ plasma concentrations. In plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins, mainly to serum albumin and $alpha_1$-acid glycoprotein.

Tacrolimus is extensively distributed in the body. The steady-state volume of distribution based on plasma concentrations is approximately 1,300 L (healthy subjects). Corresponding data based on whole blood averaged 47.6 L.

Tacrolimus is a low clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 L/hour. In adult liver, kidney and heart transplant patients, values of 4.1, 6.7 and 3.9 L/hour, respectively, have been observed. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation.

The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450 3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

Excretion

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Pharmacokinetics in special populations

The pharmacokinetics of tacrolimus in special populations have not been studied in detail. See **DOSAGE AND ADMINISTRATION** for dose adjustments in special populations.

Following oral administration of Tacrolimus Sandoz to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of tacrolimus of approximately 3.3 ng/mL was achieved within approximately 1.25 hours (T_{max}) for tacrolimus 0.5mg capsules and a mean C_{max} of tacrolimus of approximately 44 ng/mL was achieved within approximately 1.75 hours for tacrolimus 5mg capsules.

CLINICAL TRIALS

Liver. The efficacy and safety of a Tacrolimus based immunosuppressive regimen following orthotopic liver transplantation was assessed in two prospective, randomised, nonblinded multicentre trials. The active control groups were treated with a cyclosporin based regimen. In a European trial, patients received a tacrolimus steroid based regimen (n = 264) or a cyclosporin/ azathioprine/ steroid (with or without antilymphocyte globulin) based regimen (n = 265).

Equivalent graft survival (77.5 versus 72.69%) and patient survival (82.9 versus 77.5%) was seen. Significant reductions were seen in the tacrolimus treated patients for incidence of acute rejection (40.5 versus 49.8%), refractory acute rejection (0.8 versus 5.3%) and chronic rejection (1.5 versus 5.3%). In an American trial, patients received a tacrolimus steroid regimen (n = 263) or a cyclosporin (mainly triple therapy) based regimen (n = 266). Equivalent graft survival (82 versus 79%) and patient survival (88 versus 88%) rates were observed. Tacrolimus was associated with significant reductions in the incidence of acute rejection (68 versus 76%), steroid resistant rejection (19 versus 36%) and refractory rejection (3 versus 15%).

Kidney. Two randomised, multicentre nonblinded comparative trials were performed in cadaveric kidney transplantation. In an American trial, patients received a tacrolimus based (n = 205) or cyclosporin based (n = 207) regimen. All patients also received maintenance azathioprine and corticosteroids and an induction course of an antilymphocyte antibody preparation. Equivalent graft survival (91.2 versus 87.9%) and patient survival (95.6 versus 96.6%) was seen for the tacrolimus and cyclosporin treated patients, respectively. A significantly reduced one year incidence rate of biopsy confirmed acute rejection (30.7 versus 46.4%), moderate to severe acute rejection (10.7 versus 26.6%) and use of antilymphocyte antibody preparation for treatment of rejection (10.7 versus 25.1%) was seen in the tacrolimus treated patients.

A European trial compared triple drug based immunosuppression with tacrolimus or cyclosporin centred regimens, with 303 and 145 patients randomised to the tacrolimus and cyclosporin arms respectively. Equivalent one year graft survival (82.5 versus 86.2%) and one year patient survival (93.0 versus 96.5%) rates were observed, but with significantly reduced one year acute rejection rate (32.3 versus 54.5%), rate of corticosteroid sensitive rejections (24.4 versus 42.1%) and rate of corticosteroid resistant rejections (10.2 versus 20.7%).

Heart. Two open label, randomised, comparative studies evaluated the safety and efficacy of tacrolimus based and cyclosporin based immunosuppression in primary orthotopic heart transplantation. In a phase III study conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine in combination with tacrolimus or cyclosporin modified for 18 months. In a three arm study conducted in the US, 331 patients received corticosteroids and tacrolimus plus sirolimus, tacrolimus plus mycophenolate mofetil (MMF) or cyclosporin modified plus MMF for one year.

In the European phase III study, patient/ graft survival at 18 months post-transplant was similar between treatment arms, 91.7% in the tacrolimus group and 89.2% in the cyclosporin group. In the US study, patient and graft survival at 12 months was similar with 93.5% survival in the tacrolimus plus MMF group and 86.1% survival in the cyclosporin modified plus MMF group. In the European study, the cyclosporin trough concentrations were above the predefined target range (i.e. 100 to 200 nanogram/mL) at day 122 and beyond in 32 to 68% of the patients in the cyclosporin treatment arm, whereas the tacrolimus troughconcentrations were within the predefined target range (i.e. 5 to 15 nanogram/mL) in 74 to 86% of the patients in the tacrolimus treatment arm.

The US study contained a third arm of a combination regimen of sirolimus, 2mg/day, and full dose tacrolimus; however, this regimen was associated with increased risk of wound healing complications, renal function impairment and insulin dependent post-transplant diabetes mellitus, and is not recommended in *de novo* heart transplant patients (see **PRECAUTIONS**).

Lung. In a prospective, two centre, open label randomised trial, 74 lung transplant patients (aged 20 to 66 years old) were randomised to tacrolimus based (n = 37) and cyclosporin based (n = 37) immunosuppression. The drugs were given in combination with mycophenolate mofetil and corticosteroids. Tacrolimus was started immediately after transplantation as continuous intravenous infusion at a dose of 0.015mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose

adjustments to target trough levels of 12 to 15 nanogram/mL in the first month and 9 to 12 nanogram/mL thereafter. The six months and one year patient survival data was similar in both groups (89 versus 84% and 82 versus 71%, cyclosporin versus tacrolimus, respectively). Freedom from acute rejection was comparable at one year, 35% in the cyclosporin group and 46% in the tacrolimus group.

Another prospective, randomised, open label study included 66 patients on tacrolimus versus 67 patients on cyclosporin, aged 20 to 66 years old. The drugs were given in combination with azathioprine and corticosteroids. Tacrolimus was started six to eight hours after transplantation as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 nanogram/mL. The one year patient survival was 83% in the tacrolimus group and 71% in the cyclosporin group, the two year survival rates were 76 and 66%, respectively. The differences between groups were not statistically significant. Freedom from acute rejection after at least 37 weeks follow-up was also comparable (14% in the tacrolimus group and 11.5% in the cyclosporin group).

A number of published, open, uncontrolled studies have examined the use of tacrolimus in lung transplant patients who have developed refractory acute rejection or bronchiolitis obliterans syndrome while receiving cyclosporin based immunosuppressive regimens. In these studies, conversion from cyclosporin to tacrolimus has been associated with improved clinical outcomes such as reduced frequency of further acute rejection episodes and stabilisation or improvement in declining FEV_1 values.

INDICATIONS

Adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.

CONTRAINDICATIONS

Hypersensitivity to tacrolimus or other macrolides, or to other ingredients of the capsules.

PRECAUTIONS

Tacrolimus therapy requires careful monitoring in hospital units equipped and staffed with adequate laboratory and supportive medical resources. The medicine should only be prescribed, and changes in immunosuppressive therapy should be initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Post-transplant diabetes mellitus (PTDM)

Post-transplant insulin dependent diabetes mellitus (PTDM: use of insulin for 30 or more consecutive days, with < five day gap, by patients without a prior history of insulin or noninsulin dependent diabetes mellitus) was reported in 20% (30/151) and 6% (17/281) of tacrolimus treated kidney transplant patients in the US and European randomised trials,

respectively. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these patients at one year and in 50% at two years post-transplant. Black and Hispanic patients were found to be at increased risk of development of PTDM in the US trial. The risk/ benefit ratio should be carefully considered before using tacrolimus in kidney transplant patients with a pretransplant diabetic condition.

In liver transplantation PTDM was reported in 18% (42/239) and 11% (26/239) of tacrolimus treated patients and was reversible in 45 and 31% of these patients at one year post-transplant in the US and European randomised trials, respectively.

Insulin dependent post-transplant diabetes mellitus was reported in 13% (10/75) and 22% (29/132) of tacrolimus treated heart transplant patients receiving mycophenolate mofetil or azathioprine and was reversible in 30 and 17% of these patients at one year post-transplant in the US and European randomised studies, respectively.

Neurotoxicity

Neurological and CNS disorders have been reported with tacrolimus therapy. Symptoms include tremor, headache, changes in motor function, sensory function or mental status, insomnia, seizures, coma and delirium. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered.

Posterior reversible encephalopathy syndrome (PRES)

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Pure red cell aplasia (PRCA)

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

Nephrotoxicity

Tacrolimus can cause renal impairment charactered by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvements have been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of tacrolimus with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment, and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced.

Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporin. Tacrolimus or cyclosporin should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporin concentrations, dosing with the other drug usually should be further delayed.

Hyperkalaemia

Mild to severe hyperkalaemia was reported in patients treated with tacrolimus, especially in patients with renal impairment. Patients may require treatment and should avoid high dietary potassium intake. Serum potassium levels should be monitored and potassium sparing diuretics should not be used during tacrolimus therapy.

Vaccinations

As with other immunosuppressants, response to vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Gastrointestinal disorders

Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments including surgery should be considered immediately after a suspect symptom occurs.

Potential Interactions

When substances with a potential for interaction (see **INTERACTIONS WITH OTHER MEDICINES**) – particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Malignancies

As with other potent immunosuppressive compounds, patients treated with tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disorder (LPD) related to Epstein-Barr virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. In patients switched to tacrolimus, this may be attributable to over immunosuppression before commencing therapy with this agent. Very young (< 2 years), EBV seronegative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient

group, EBV serology should be ascertained before starting treatment with tacrolimus. During treatment, careful monitoring is recommended.

Infections

Like other immunosuppressants, tacrolimus predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections. Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections. Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Hypertension

Hypertension is a common adverse effect of tacrolimus therapy. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalaemia, potassium sparing diuretics should be avoided. While calcium channel blocking agents can be effective in treating tacrolimus associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Myocardial hypertrophy

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies have been observed in a few cases in association with administration of tacrolimus. Most of these have been reversible, occurring primarily in patients having tacrolimus blood trough levels higher than the recommended level. Mean tacrolimus whole blood trough concentrations during the period prior to diagnosis of myocardial hypertrophy in 20 patients with pretreatment and post-treatment echocardiograms ranged from 10.6 to 53.3 nanogram/mL in infants (n = 10, age 0.4 to 2 years), 4.0 to 45.7 nanogram/mL in children (n = 7, age 2 to 15 years) and 10.9 to 24.3 nanogram/mL in adults (n = 3, age 37 to 45 years). Other factors observed to increase the risk of these clinical conditions are, for example, previously existing heart diseases, corticosteroid usage, hypertension, renal or hepatic dysfunction and fluid overload. Accordingly, high risk patients should be monitored, e.g. with echocardiography or ECG. If abnormalities develop, dose reduction of tacrolimus therapy or change of treatment to other immunosuppressive agent should be considered.

QT Interview Prolongation

Tacrolimus may prolong the QT interval and may cause Torsade de Pointes. Caution should be exercised in patients with known risk factors for QT prolongation (including, but not limited to, congenital or acquired QT prolongation, concomitant medications known to prolong the QT interval or known to increase tacrolimus exposure).

Conversion between tacrolimus formulations

Various dosage forms of tacrolimus are available, including immediate release oral dosage forms, prolonged release dosage forms and injectable dosage forms*. Medication errors have resulted in incorrect dosing or unsupervised switching between tacrolimus dosage forms. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under exposure or over exposure to tacrolimus. Therefore, it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (i.e. tacrolimus immediate release capsules– twice daily dosing). It should be emphasised that patients, once titrated to an effective dose of a particular dosage form of tacrolimus, should not be changed to another dosage form of tacrolimus without blood trough level monitoring, clinical assessment and re-titration (see **DOSAGE AND ADMINISTRATION**).

*Not all dosage forms are marketed by Sandoz but are available in other brands.

Conversion from cyclosporin

Tacrolimus should not be administered concurrently with cyclosporin as the half-life of the latter may be increased. Synergistic/ additive nephrotoxic effects can also occur. Care should be taken when administering tacrolimus to patients who have previously received cyclosporin and when converting patients from cyclosporin- to tacrolimus- based therapy. It is recommended that cyclosporin blood levels are monitored prior to the administration of tacrolimus. The most appropriate time to initiate tacrolimus therapy should be based upon information on cyclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated cyclosporin levels. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected. A 24 hour interval between stopping cyclosporin and starting tacrolimus has been commonly used.

Patients switched to tacrolimus rescue therapy should not be given antilymphocyte treatment concomitantly.

Renal insufficiency

Tacrolimus can cause renal impairment characterised by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvement has been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of tacrolimus with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced.

Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporin. Tacrolimus or cyclosporin should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporin concentrations, dosing with the other drug usually should be further delayed.

Hepatic insufficiency

Tacrolimus is extensively metabolised by the liver. In patients with liver impairment, dose reduction is recommended.

Driving / Operation of Machinery
Tacrolimus may cause visual and neurological disturbances. Patients treated with tacrolimus who are affected by such disorders should not drive a car or operate dangerous machinery. This effect may be enhanced if tacrolimus is administered in association with alcohol.

Effects on fertility
Oral treatment of rats with tacrolimus had no effect on male or female fertility at oral doses up to 3.2mg/kg (blood exposure was less than the exposure achieved after the maximum recommended clinical dose, 0.3mg/kg, based on AUC).

Use in pregnancy (Category C)

In reproduction studies in rats and rabbits, adverse effects on the foetus were observed mainly at dose levels that were toxic to the dams. Tacrolimus at oral doses of 0.32 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in the incidence of abortions. At 1.0mg/kg increased incidences of malformations and developmental variations were also seen (a dose of 1.0mg/kg resulted in a blood exposure approximately equivalent to the exposure achieved after the maximum recommended clinical dose, 0.3mg/kg, based on AUC). Tacrolimus, at oral doses of 3.2mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births and decreased pup weight and viability (a dose of 3.2mg/kg resulted in a blood exposure less than the exposure achieved after the maximum recommended clinical dose, 0.3mg/kg, based on AUC). Tacrolimus, given orally at 1.0 and 3.2mg/kg to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights. No reduction in male or female fertility was evident.

There are no adequate and well controlled studies in pregnant women. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalaemia and renal dysfunction. There is a risk for premature delivery. Cases of spontaneous abortion have been reported. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the foetus.

Use in lactation

Tacrolimus is excreted into breast milk. It is, therefore, recommended that mothers should not breastfeed while receiving tacrolimus.

Carcinogenicity

Tacrolimus did not show any tumorigenic effects in long-term carcinogenicity studies using the mouse and rat. The maximum dose tested in the rat resulted in a blood exposure less than, and a plasma exposure 1.4 times, the exposure achieved after the maximum recommended clinical dose, 0.3mg/kg, based on area under the curve (AUC). In mice the maximum dose was 0.8 times the recommended clinical dose based on body surface area.

Patients receiving long-term immunosuppressive therapy are at an increased risk of developing lymphomas and other malignancies (see **PRECAUTIONS**, Malignancies).

Genotoxicity

No evidence of genotoxicity was seen in a series of assays for gene mutations and clastogenicity. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes but high concentrations of tacrolimus have been reported to increase the frequency of sister chromatid exchanges in human lymphocytes *in vitro.*

INTERACTIONS WITH OTHER MEDICINES

Metabolic interactions

Drug(s)	Observation	Clinical Significance
drugs or herbal remedies known to inhibit or induce CYP3A4	Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.	It is therefore recommended to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effect, whenever drugs which have the potential to alter CYP3A metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of metabolism

Clinically the following substances have been shown to increase tacrolimus blood levels:

Drug(s)	Observation	Clinical Significance
antifungal agents such as ketoconazole, fluconazole, itraconazole, voriconazole; erythromycin (macrolide antibiotic); HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir) and amiodarone.	Strong interactions have been observed.	Concomitant use of these drugs may require decreased tacrolimus doses in nearly all patients.
clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole, nefazodone	Weaker interactions have been observed.	Concomitant use of these drugs may require monitoring of tacrolimus levels.
herbal remedy schisandra sphenanthera extract	Inhibits CYP3A4	Concomitant use may increase blood levels of tacrolimus.
bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl)oleandomycin	Potential inhibitor of tacrolimus metabolism *in-vitro*.	
grapefruit juice	Reports of the blood level of tacrolimus increased.	Concomitant use should therefore be avoided.

lansoprazole	May potentially inhibit CYP3A4-mediated metabolism and thereby increase tacrolimus whole blood concentrations.	
cyclosporin	May potentially inhibit CYP3A4-mediated metabolism and thereby increase tacrolimus whole blood concentrations.	Concomitant use is not recommended. See table – Effect of tacrolimus on the metabolism of other drugs.

Inducers of metabolism

Clinically the following substances have been shown to decrease tacrolimus blood levels:

Drug(s)	Observation	Clinical Significance
rifampicin, phenytoin or St John's Wort (*Hypericum perforatum*)	Strong interactions have been observed.	Increased tacrolimus doses may be required in almost all patients.
phenobarbital	Clinically significant interactions have also been observed.	
maintenance doses of corticosteroids	Tacrolimus blood levels reduced.	
high dose prednisolone or methylprednisolone administered for the treatment of acute rejection	Potential to increase or decrease tacrolimus blood levels.	
Carbamazepine, metamizole, isoniazid	Potential to decrease tacrolimus concentrations.	

Effect of tacrolimus on the metabolism of other drugs:

Drug(s)	Observation	Clinical Significance
drugs known to be metabolised by CYP3A4	Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with drugs known to be metabolised by CYP3A4 may affect the metabolism of such drugs.	
cyclosporin	The half-life of cyclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur.	For these reasons, the combined administration of cyclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporin.
phenytoin	Tacrolimus have been shown to increase the blood level of phenytoin.	
steroid-based contraceptives	Tacrolimus may reduce the clearance of steroid-based contraceptives, leading to increased hormone exposure.	Particular care should be exercised when deciding upon contraceptive measures.
statins	Limited knowledge of interactions between tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins	

	are largely unaltered by the co-administration of tacrolimus.	
pentobarbital, antipyrine	Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.	

Other potential interactions that may increase systemic exposure of tacrolimus:

- prokinetic agents such as metoclopramide and cisapride
- cimetidine
- magnesium-aluminium-hydroxide.

Other interactions which have led to clinically detrimental effects:

Drug(s)	Observation	Clinical Significance
drugs known to have nephrotoxic or neurotoxic effects (e.g. aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir)	Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase these effects.	
amphotericin B and ibuprofen	Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.	
high potassium intake or potassium-sparing diuretics (e.g. amiloride, triamterene or spironolactone)	Tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia.	Concomitant use should be avoided.
live attenuated vaccines	Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective.	The use of live attenuated vaccines should be avoided.

Protein binding considerations:

Drug(s)	Observation	Clinical Significance
drugs known to have high affinity for plasma proteins (e.g. NSAIDs, oral anticoagulants or oral antidiabetics)	Tacrolimus is extensively bound to plasma proteins.	Possible interactions with other drugs known to have high affinity for plasma proteins should be considered.

ADVERSE EFFECTS

The adverse drug effect profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications.

The most commonly reported adverse drug reactions (occuring in >10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

Many of the adverse drug effects stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse drug effects compared with intravenous use. Adverse drug effects are listed below in descending order by frequency of occurrence: very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000, including isolated reports).

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, include tacrolimus.

Neoplasms benign, malignant and unspecified

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

Common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal.
Uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia.
Rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia.
Unknown frequency: Pure red cell aplasia (observed during post-marketing), agranulocytosis, haemolytic anaemia.

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see **PRECAUTIONS**).

Endocrine disorders

Rare: hirsutism.

Metabolism and nutrition disorders

Very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia.
Common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic

acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities.
Uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia.

Psychiatric disorders

Very common: insomnia.
Common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders.
Uncommon: psychotic disorder.

Nervous system disorders

Very common: tremor, headache.
Common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders.
Uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia.
Rare: hypertonia.
Very rare: myasthenia.

Eye disorders

Common: vision blurred, photophobia, eye disorders.
Uncommon: cataract.
Rare: blindness.

Ear and labyrinth disorders

Common: tinnitus.
Uncommon: hypoacusis.
Rare: deafness neurosensory.
Very rare: hearing impaired.

Cardiac disorders

Common: ischaemic coronary artery disorders, tachycardia.
Uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations, QT prolongation, torsades de pointes.
Rare: pericardial effusion.
Very rare: abnormal echocardiogram.

Vascular disorders

Very common: hypertension.
Common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders.

Uncommon: infarction, venous thrombosis deep limb, shock.

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations.
Uncommon: respiratory failures, respiratory tract disorders, asthma.
Rare: acute respiratory distress syndrome.

Gastrointestinal disorders

Very common: diarrhoea, nausea.
Common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms.
Uncommon: paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastroesophageal reflux disease, impaired gastric emptying.
Rare: subileus, pancreatic pseudocyst.

Hepatobiliary disorders

Very Common: liver function test abnormal
Common: bile duct disorders, cholestasis and jaundice, hepatocellular damage and hepatitis.
Rare: hepatic artery thrombosis, veno-occlusive liver disease.
Very rare: hepatic failure, bile duct stenosis

Skin and subcutaneous disorders

Common: pruritus, rash, alopecias, acne, sweating increased.
Uncommon: dermatitis, photosensitivity.
Rare: toxic epidermal necrolysis (Lyell's syndrome).
Very rare: Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle cramps, pain in limb, back pain.
Uncommon: joint disorders.

Renal and urinary disorders

Very common: renal impairment.
Common: renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms.
Uncommon: anuria, haemolytic uraemic syndrome.
Very rare: nephropathy, haemorrhagic cystitis.

Reproductive system and breast disorders

Uncommon: dysmenorrhoea and uterine bleeding.

General disorders and administration site conditions

Common: asthenic conditions, febrile disorders, oedema, pain and discomfort, increased blood alkaline phosphatase, increased weight, disturbed body temperature perception.
Uncommon: multiorgan failure, influenza-like illness, temperature intolerance, chest pressure sensation, feeling jittery, abnormal feeling, increased blood lactate dehydrogenase, decreased weight.
Rare: thirst, fall, chest tightness, decreased mobility, ulcer.
Very rare: increased fat tissue.

Injury, poisoning and procedural complications

Common: primary graft dysfunction.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

DOSAGE AND ADMINISTRATION

The dosage recommendations given below for oral administration should act as a guideline. Tacrolimus doses should be adjusted according to individual patient requirements.

Use in transplants

*Liver transplantation***.** Tacrolimus therapy should commence at 0.10 to 0.20 mg/kg/day administered as two divided doses. Administration should start approximately six hours after the completion of liver transplant surgery.

Kidney transplantation. Tacrolimus therapy should commence at 0.15 to 0.30 mg/kg/day administered as two divided doses. Administration should start within 24 hours of kidney transplant surgery.

Lung transplantation. Tacrolimus therapy should commence at 0.10 to 0.30 mg/kg/day administered as two divided doses. Administration should start within 24 hours of lung transplant surgery.

Heart transplantation. Tacrolimus therapy should commence at 0.075mg/kg/day administered as two divided doses. Administration should start within 24 hours of heart transplant surgery.

Infants and children
Higher mg/kg doses may be required in children compared with adults to achieve the same tacrolimus blood concentration
Therapy dose levels for kidney, liver, lung or heart allograft rejection resistant to existing immunosuppressive regimens

In patients experiencing rejection episodes which are unresponsive to conventional immunosuppressive therapy. Tacrolimus treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

Conversion between tacrolimus formulations

Differences between oral dosage forms of tacrolimus can lead to important differences in system exposure to tacrolimus. Inadvertent or unsupervised switching between dosage forms is unsafe and could lead to graft rejection or increased incidence of side effects. Therefore, it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (i.e. tacrolimus immediate release capsules– twice daily dosing). Patients must only be switched from one tacrolimus dosage form to another under the close supervision of a transplant specialist.

Conversion from cyclosporin to tacrolimus

Care should be taken when converting patients from cyclosporin-based to tacrolimus-based therapy (see **PRECAUTIONS** and -**INTERACTIONS WITH OTHER MEDICINES**). Tacrolimus-based therapy should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12-24 hours after discontinuation of cyclosporin. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin might be affected.

Use in the elderly

Experience in the elderly is limited. There is no evidence presently available to suggest that doses should be altered in elderly patients.

Use in patients with renal insufficiency

No dose adjustment is required. However, careful monitoring of renal function is recommended.

Use in patients with hepatic insufficiency

Tacrolimus is extensively metabolised by the liver. In patients with liver impairment dose reduction is recommended.

Tacrolimus is normally administered together with other immunosuppressive drugs. In isolated cases, successful maintenance therapy with tacrolimus alone has been described. Tacrolimus should not be given concurrently with cyclosporin.

If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Administration of Tacrolimus Sandoz should commence as soon as practicable. In some liver transplantation patients, therapy has commenced orally by administering the capsule contents suspended in water, via an intranasal gastric tube.

It is recommended that the oral daily dose be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. The capsules should be taken on an empty stomach or at least one hour before or two to three hours after a meal to achieve maximal absorption.

Race

In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender

There is no evidence that male and female patients require different doses to achieve similar trough levels.

Monitoring advice

Monitoring of tacrolimus whole blood trough concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood trough concentration monitoring is not a replacement for renal or liver function monitoring and tissue biopsies.

Various assays have been used to measure blood or plasma concentrations of tacrolimus. Comparison of the concentrations in published literature to patient concentrations should be made with care and knowledge of the assay methods employed.

The majority of patients (adults and children) can be successfully managed if the trough (12 hour) blood concentrations are maintained within the following range.

Liver transplant: 5 to 20 nanogram/mL for the first three months, 5 to 15 nanogram/mL thereafter.

Kidney transplant: 10 to 20 nanogram/mL for the first three months, 5 to 15 nanogram/mL thereafter.

Heart transplant: 10 to 20 nanogram/mL for the first three months, 5 to 15 nanogram/mL thereafter.

Lung transplant: 10 to 20 nanogram/mL for the first month, then 5 to 15 nanogram/mL thereafter.

During the first months post-transplant, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, visual status, blood glucose levels, electrolytes (particularly potassium), creatinine, blood urea nitrogen, urinary output, haematology parameters, coagulation values, and liver and renal function tests. If clinically relevant changes are seen, adjustment of the immunosuppressive regimen should be considered.

Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus. This should be considered when deciding upon a maintenance regimen.

Compatibility

Tacrolimus is incompatible with PVC plastics. Tubing, syringes, and other equipment used to administer tacrolimus should not contain PVC.

OVERDOSAGE

Contact the Poisons Information Centre (Australia 13 11 26 or New Zealand 0800 764 766) for advice on management of overdose.

Symptoms

Experience of overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels.

Early clinical experience (when initial induction doses were two to three times greater than those currently recommended) suggested that symptoms of overdosage may include glucose intolerance, renal, neurological and cardiac disorders, hyperkalaemia and hypertension. Over immunosuppression may increase risk of severe infections.

Liver function clearly influences all pre- and postoperative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to tacrolimus should be monitored carefully to avoid overdosage.

Treatment

No specific antidote to tacrolimus therapy is available. If overdosage occurs, general supportive measures and symptomatic treatment should be conducted.

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus will not be dialysable. Data on haemoperfusion are not available. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex,

consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

PRESENTATION AND STORAGE CONDITIONS

Tacrolimus Sandoz 0.5mg: White to off-white powder filled in size "4" capsule with white coloured opaque body and ivory coloured cap.

*Tacrolimus Sandoz 0.75mg: White to off-white powder filled in size "4" capsule with light green opaque body and cap, imprinted in black with 0.75 mg on cap.

Tacrolimus Sandoz 1mg: White to off-white powder filled in size "4" capsule with white coloured opaque body and light brown coloured cap.

*Tacrolimus Sandoz 2mg: White to off-white powder filled in size "4" capsule with dark green opaque body and cap, imprinted in black with 2 mg on cap.

Tacrolimus Sandoz 5mg: White to off-white powder filled in size "3" capsule with white coloured opaque body and Swedish orange coloured cap.

Tacrolimus Sandoz is packed in PVC/PE/PVdC/Al blister with aluminium wrapping

Available in packs of 100 capsules (0.5mg/1mg) or 50 capsules (5mg)
Available in packs 7, 10, 14, 20, 28, 30, 50, 60, 90 and 100 capsules (0.75 mg / 2 mg)

Store below 30°C. Store in original container. After opening of the aluminium wrapping, store below 25°C and use within twelve months. Do not use after printed expiry date.

**Note that these strengths are only available in Australia*
Not all strengths are available in New Zealand

NAME AND ADDRESS OF THE SPONSOR

Australia
Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road,
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

New Zealand
Novartis New Zealand Ltd
PO Box 99102
Newmarket
Auckland 1149
Tel: 0800 354 335

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 15/02/2010

Date of most recent amendment: 24/08/2017